10/758,253

PTO 06-2757

CY=FR DATE=19730601 KIND=A1
PN=2,156,486

OXAZOLE DERIVATIVES, SALTS AND ESTERS THEREOF, METHOD OF PRODUCTION AND USE IN MEDICATIONS

[DERIVES DE L'OXAZOLE, LEURS SELS ET ESTERS, PROCEDE DE PREEPARATION ET APPLICATION A TITRE DE MEDICAMENTS]

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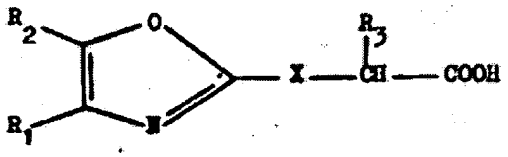
UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. March 2006

Translated by: FLS, Inc.

PUBLICATION COUNTRY	(10):	FR
DOCUMENT NUMBER	(11):	2,156,486
DOCUMENT KIND	(12):	A1
PUBLICATION DATE	(41):	19730601
APPLICATION NUMBER	(21):	71.38043
APPLICATION DATE	(22):	19711022
INTERNATIONAL CLASSIFICATION	(51):	A61K 27/00 // C07D 85/00
PRIORITY COUNTRY	(33):	NA
PRIORITY NUMBER	(31):	NA
PRIORITY DATE	(32):	NA
INVENTOR	(72):	NA
APPLICANT	(71):	ROUSSEL-UCLAF
TITLE	(54):	OXAZOLE DERIVATIVES, SALTS AND ESTERS THEREOF, METHOD OF PRODUCTION AND USE IN MEDICATIONS
FOREIGN TITLE	[54A]:	DERIVES DE L'OXAZOLE, LEURS SELS ET ESTERS, PROCEDE DE PREEPARATION ET APPLICATION A TITRE DE MEDICAMENTS

Description /1*

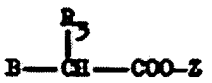
The present invention, to the development of which Mr. Pierre-Henri Derible and Mr. Laurent Taliani contributed, concerns new oxazole derivatives, as well as metallic salts thereof, addition salts thereof with nitrogenated bases, and esters thereof with alcohols containing at most 4 carbon atoms, these derivatives being characterized by corresponding to the following general formula:



(I)

in which X represents an oxygen or sulfur atom, R_1 represents a hydrogen atom, or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, R_2 represents a hydrogen atom or an alkyl radical containing at most 3 carbon atoms or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, and R_3 represents a hydrogen atom, or an alkyl radical containing at most 3 carbon atoms.

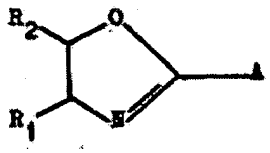
The invention also concerns the method of producing derivatives of general formula I, wherein a product of the formula is sodafied:



(II)

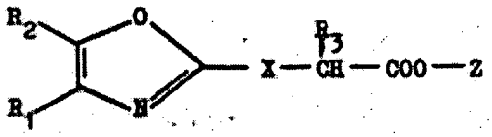
*Numbers in the margin indicate pagination in the foreign text.

in which B represents an -OH radical or an -SH radical, Z represents an alkyl radical containing at most 4 carbon atoms and R_3 has the meaning already indicated, then this sodafied product is made to react with a product of the formula:



(III)

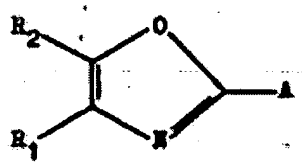
in which R_1 and R_2 have the meaning already indicated and A represents a chlorine atom, then an alkaline hydroxyl is used to hydrolyze the product of the following formula: /2



(IV)

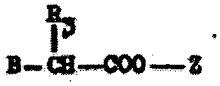
in which R_1, R_2, R_3, X, and Z have the meaning already indicated, thus obtained, in order to obtain the product of formula I.

According to one version of the process applicable to the production of the products of formula I in which x represents a sulfur atom, the method is characterized by the fact that a product of the following formula is sodafied:



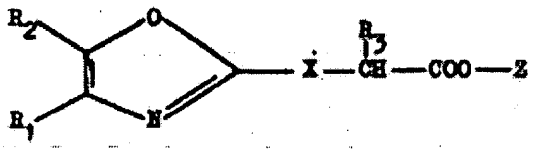
(III)

in which R_1 and R_2 have the meaning already indicated and A represents a radical -SH, then by the fact that this sodafied product can be made to act with a product of the following formula:



(II)

in which R represents a chlorine or bromine atom, Z represents an alkyl radical including at most 4 carbon atoms, and R_3 has the meaning already indicated, then the product of the following formula is hydrolyzed by means of an alkaline hydroxide :



(IV)

in which R_1, R_2, R_3, X, and Z have the meaning already indicated, thus obtained, in order to obtain the product of formula I.

The object of the invention also is the process of producing metallic salts and addition salts with the nitrogenated bases of derivatives of formula I, a process characterized by the fact that mineral bases or corresponding nitrogenated bases is made to act on these derivatives of formula I.

The invention also concerns the process of production of esters with alcohols containing at most 4 carbon atoms of derivatives of Formula I, a method in which an alcohol containing at most 4 carbon /3 atoms in the presence of an acid catalyst is made to act on these derivatives.

Also according to the invention, the esters of derivatives of formula I can be obtained by isolating, at the time of the production of derivatives of formula I, the esters of formula IV described above.

The invention also concerns application to medications and in particular anti-inflammatory, analgesic, and anti-pyretic medications,

derivatives of formula I, pharmaceutically acceptable metallic salts thereof, addition salts thereof with nitrogenated bases, and esters thereof with alcohols containing at most 4 carbon atoms.

Finally, the invention concerns the pharmaceutical compositions that contain at least one above-mentioned derivative as active principle.

In using the process of producing derivatives of formula I, preferably the following procedure is followed:

a) at the beginning of the operation, the one of the two products of formula II or II in which A or B represents an -OH radical or an -SH radical is sodified with sodium ethylate or sodium hydride;

b) when a product of formula II in which B represents an -OH radical or an -SH radical is used, the mixture of the sodified derivative of the product of formula II and the product of formula III in which A represents a chlorine atom, within an organic solvent such as dimethyl formamide or toluene is held from one to ten hours at a temperature between ambient temperature and the boiling temperature;

c) when a product of formula II in which A represents an -SH radical is used, the mixture of the sodified derivative of the product of formula III and the product of formula II, in which B represents a chlorine or bromine atom, in an organic solvent such as dimethyl formamide or toluene, is held from one to ten hours at a temperature between ambient temperature and the boiling temperature;

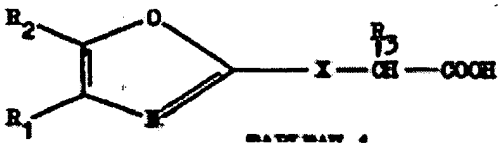
d) the product of formula IV is hydrolyzed by means of sodium hydroxide in order to obtain the product of formula I.

Advantageously, it is possible to produce salts of derivatives of formula I by making the mineralized or nitrogenated bases react in approximately stoichiometric proportions with these derivatives of formula I, by operating in the presence of water or an aliphatic /4 alcohol of low molecular weight.

Advantageously, it is possible to produce esters of derivatives of formula I by making the derivatives of formula I react with alcohols in organic solvents that may consist of the alcohols themselves; sulfuric acid or hydrochloric acid is used as an acid catalyst, and the process is performed at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

The products of formula I, salts thereof and esters thereof are very useful substances for medications, in particular because of their very interesting anti-inflammatory, analgesic, and anti-pyretic properties. Pharmacological investigation thereof has made it possible to demonstrate their great activity and very interesting nature.

More particularly, the items indicated in Table 1 below were tested.



(I)

TABLE 1

N° de référence des produits étudiés	X	R_1	R_2	R_3
1285-01	S	C_6H_5	C_6H_5	H
1285-02	O	C_6H_5	C_6H_5	H
1285-03	S	$pCl-C_6H_4$	H	H
1285-04	S	$pCH_3O-C_6H_4$	$pCH_3O-C_6H_4$	H
1285-05	S	$pCl-C_6H_4$	CH_3	H
1285-06	O	$pCH_3O-C_6H_4$	$pCH_3O-C_6H_4$	CH_3
1285-07	S	H	$pCl-C_6H_4$	H
1285-08	O	$pCH_3O-C_6H_4$	$pCH_3O-C_6H_4$	H
1285-09	O	$pCl-C_6H_4$	CH_3	H
1285-10	O	$pCl-C_6H_4$	H	H
1285-11	O	$pCl-C_6H_4$	$pCl-C_6H_4$	H

Key:

Reference No. of products studied				

The pharmacological results obtained with the products designated above are shown below:

1) The anti-inflammatory activity has been evaluated vis-a-vis /5 a carragenin abcess according to the BENITZ and HALI technique (Arch. Inter. Pharmacodyn. Therap. 1963, 144, 185) with the following protocol:

Male rats weighing around 160 g were separated into groups of 5 animals each. All the animals received subcutaneously 0.5 ml of a 2% carragenin solution in a physiological solution in the dorso-lumbar region.

The compounds to be studied, suspended in a 5% solution of gum Arabic, were administered orally, a control group receiving only the vehicle. The total dose administered was 200 mg/kg; it was divided

into two half-doses ingested one in the morning at the same time as the injection of carragenin, the other in the afternoon around six hours later, the volume each time being 0.5 ml/100 g of body weight.

Twenty-four hours after the injection of carragenin, the animals were killed by chloroform inhalation. Then the skin of the dorsal region was turned back and the abcess formed was removed. The exudate and the gelatinous substance isolated were immediately weighed.

The activity of the compounds is indicated by the percentage of inhibition of the average weight of the abcesses removed from the animals treated with respect to that of the abcesses removed from the control animals.

The results obtained are shown in Table 2 below:

TABLE 2

N° de référence des produits étudiés	Pourcentage d'inhibition de l'abcès à la carragénine	N° de référence des produits étudiés	Pourcentage d'inhibition de l'abcès à la carragénine
1285-01	25	1285-07	42
1285-02	18	1285-08	50
1285-03	37	1285-09	30
1285-04	45	1285-10	53
1285-05	23	1285-11	35
1285-06	37		

Key:

Reference No. of products studied	Percentage of inhibition of the abcess due to carragenin	Reference No. of products studied	Percentage of inhibition of the abcess due to carragenin

2) The anti-inflammatory activity also was investigated vis-a-vis the edema to carragenin according to the technique of WINTER et coll. (Proc. Soc. Exp. Biol. Med. 1962, 111, 544). The compounds were

administered orally, suspended in a 5% solution of gum arabic, in a dose of 200 mg/kg in groups of 5 male rats each weighing around 150 g. The ingested volume is 0.5 ml/100 g of body weight. One hour after the force-feeding, the thickness of the right rear foot was measured, then 0.05 ml of a 1% solution of carragenin in physiological solution was injected into the plantar pad. Three hours later, the thickness of the treated foot was measured again. The difference between the two measurements indicates the amount of the edema caused by the carragenin. /6

The measurements performed in parallel in the control animals having received only the vehicle of administration of the products tested and the injection of carragenin made it possible to evaluate the percentage of inhibition of the average edema observed in the animals treated.

The results obtained are given in Table 3 below:

TABLE 3

N° de référence des produits étudiés	Pourcentage d'inhibition de l'oedème à la carragénine	N° de référence des produits étudiés	Pourcentage d'inhibition de l'oedème à la carragénine
1285-03	21	1285-08	39
1285-04	41	1285-09	41
1285-05	23	1285-10	56
1285-06	19		

Key:

Reference No. of products studied	percentage of inhibition of edema due to carragenin	Reference No. of products studied	percentage of inhibition of edema due to carragenin

3) The anti-inflammatory activity also was investigated vis-a-vis the erythema caused by ultraviolet radiation, according to the

technique of WINDER, et coll. (Arch. Int. pharmacodyn. 1958, 1167, 261).

The night before the test, the hair on the dorsal region of 300 g white Hartley guinea pigs was clipped and removed by application of a depilatory cream. At the zero time, the compounds were administered in gel capsules orally in a dose of 100 mg/kg. One hour after, the animals were irradiated for forty-five seconds by a UV lamp in the following conditions: the radiation source was around 3 cm from a metal box pierced by 4 circular holes 5 mm in diameter, which was applied directly to the depilated skin of the guinea-pig. (This device makes it possible to obtain 4 erythematous spots).

Four hours after the irradiation, a score of 0 - 0.5 or 1 was attributed to each spot according to the intensity of the reaction /7 as compared with that observed in the controls. (It is considered that an animal is protected if the total of the scores that are attributed to it is less than or equal to 2).

The results obtained showed a total protection of the guinea pigs treated with 1285-01, 1285-04, 1285-08, 1285-09, 1285-10, and 1285-11.

4) The analgesic power was investigated in mice by means of the phenyl benzoquinone test according to the technique of Siegmund et coll. (Proc. Soc. Exper. Biol. Med. 1957, 95, 729).

The protection provided by the administration of the products studied was evaluated in percentage according to the following formula:

% of protection = 100 [1- number of stretchings of the animals treated

/ number of stretchings of the control animals]

The results obtained are shown in Table 4 below:

Table 4

N° de référence des produits étudiés	Pourcentage de protection vis-à-vis de la phénylbenzoquinone aux doses de :	
	50 mg/kg (per os)	12,5 mg/kg (per os)
1285-01	73	-
1285-02	83	81
1285-03	34	4
1285-04	93	68
1285-05	24	21
1285-06	86	77
1285-07	56	38
1285-08	94	77
1285-09	64	78
1285-10	100	82
1285-11	100	100

Key:

Reference No. of products studied	Percentage of protection vis-a-vis phenyl benzoquinone to doses of:	
	50 mg/kg (per os)	12.5 mg/kg (per os)

5) The analgesic power also has be investigated in mice by means of the EDDY test. The results obtained showed that at a dose of 200 mg/kg certain compounds very appreciably increased the normal pain reaction time.

The results obtained are given in Table 5 below:

TABLE 5 /8

N° de référence des produits étudiés	Pourcentage d'augmentation du temps normal de réaction à la douleur :
1285-01	21
1285-02	40
1285-07	15
1285-08	13
1285-09	24
1285-11	35

Key:

Reference No. of products studied	Percentage of increase of the normal pain reaction time

6) The anti-pyretic power was used for evaluation the antagonism of the products in the rat vis-a-vis the pyrexia caused by the sub-cutaneous injection of a beer yeast suspension (1 ml/100 g of body weight of a 15% beer yeast suspension in a 1% aqueous solution of gum tragacanth). The compounds studies were administered orally in a dose of 200 mg/kg three hours after the injection of beer yeast. The percentage of inhibition of the experimental hyperthermia was expressed as follows:

$$\% \text{ of inhibition} = 100 \left[1 - \frac{\text{,) animals treated}}{\text{,) animals treated}}\right]$$

) being the average of the hourly algebraic variation of individual rectal temperature with respect to the initial rectal temperature, the temperatures being monitored from hour to hour during the seven hours that the test lasts.

The percentages of inhibition of pyrexia are given in Table 6 below:

TABLE 6

N° de référence des produits étudiés	Pourcentage d'inhibition de la pyrexie
1285-03	13
1285-04	36
1285-06	40
1285-08	76
1285-09	45
1285-11	15

Key:

Reference No. of products studied	Percentage of inhibition of pyrexia

The lethal doses 50 of the compounds tested, evaluated orally /9 in mice where found: greater than 1,600 mg/kg for compound 1285-01, between 800 and 1,600 mg/kg for compounds 1285-01, 1285-02, 1285-03, 1285-05, 1285-06, 1285-07 and 1285-08, between 400 and 800 mg/kg for compounds 1285-04, 1285-10, and 1285-11.

Because of their remarkable pharmacological properties, the products of formula I as well as their pharmaceutically acceptable metallic salts of addition with the nitrogenated bases and pharmaceutically acceptable esters thereof with alcohols contain at most 4 carbon atoms, according to the invention constitute very useful medications in human therapeutics, in particular in the treatment of acute and chronic rheumatism, different algias, and febrile illnesses. The usual dose, variable according to the product used, the subject treated, and the causal disease, can be, for example, 100 mg to 1 g per day orally in man.

The metallic salts can be, for example, salts of alkaline metals, such as sodium, potassium, or lithium, alkaline-earth metals, such as

calcium or magnesium, or metals such as aluminum. The salts of nitrogenated bases can be ammonium salts or salts of aliphatic, aryl aliphatic, or heteroalkoyl aliphatic amines.

The esters can be, for example, esters with ethanol, propanol, or butanol.

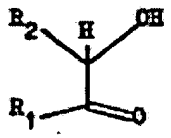
The invention also concerns pharmaceutical compositions containing as active principle the oxazole derivatives of formula I and/or salts thereof and/or pharmaceutically acceptable esters thereof. These compositions are made so as to be able to be administered by digestive, parenteral, or local paths. They can be solid or liquid and are presented in the pharmaceutically forms currently used in human medicine, such as, for example, simple or dragee tablets, gel capsules, granules, suppositories, injectable products, ointments, creams, or gels; they are produced according to the usual methods. The active principle or principles can be incorporated with the excipients habitually used in these pharmaceutical compositions, such as talk, gum arabic, lactose, starch, magnesium stearate, cacao butter, aqueous or non-aqueous vehicles, fats of animal or plant origin, paraffin derivatives, /10 glycols, different softening, dispersing, or emulsifying agents, and preservatives.

To the applicant's knowledge, certain compounds, necessary for the production of the products according to the invention, have not yet been described. The invention also extends to these new compounds, and, in particular, to the following products of formula

III: chloro-2-bis (paramethoxyphenyl)-4,5 oxazole, chloro-2 parachlorophenyl-4 methyl-5 oxazole, chloro-2 parachlorophenyl-4 oxazole, chloro-2 bis (parachlorophenyl)-4,5- oxazole, parachlorophenyl-4 mercapto-2 oxazole, parachlorophenyl-4 mercapto-2 methyl-5 oxazole, parachloropheyyl-5 mercapto-2 oxazole.

The products of formula III, when they are not known, can be produced as follows:

A product of formula:

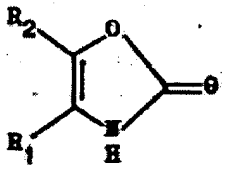


(V)

in which R_1 and R_2 have the meaning already indicated,

is acted upon

- either by ethyl carbamate for forming a product of the following formula:



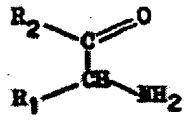
(VI)

in which R_1 and R_2 have the meaning already indicated, a product that is made to act with phosphorous oxychloride in order to obtain a product of formula III in which A represents a chlorine atom,

- or by potassium thiocyanate suspended in ethanol in order to obtain a product of formula III in which A represents a radical -SH.

According to a version of the process of producing products of formula III in which A represents a radical -SH, it is also possible

to treat a product of formula:



(VII)

in which R_1 and R_2 have the meaning already indicted, with carbon sulfide, in order to obtain a product of formula III in which A represents a radical -SH. An example of such products is given below in the examples. /11

Non-limiting examples of embodiments will now be given.

Example 1: (diphenyl-4,5 oxazolyl)-2 thio /acetic acid:

A solution of 12 g (0.1 mole) of mercapto-2 ethyl acetate in 50 ml of anhydrous toluene is added to a sodium ethylate solution produced from 2.3 g (0.1 at. g) of sodium and 100 ml of absolute ethanol. The solution is concentrated under a vacuum and 200 ml anhydrous toluene is added. A solution of 26 g (0.12 mole) of chloro-2 diphenyl-4,5 oxazole in 50 ml of anhydrous toluene is added to the suspension obtained. The mixture is brought to boiling with reflux for three hours, and is cooled, the solution is washed in water, and dried, and the solvent is eliminated under reduced pressure.

30.3 g of an oil is obtained, which is brought to boiling with reflux for two hours in a mixture of 200 ml of 95° ethanol and 4 g (0.1 mole) of sodium hydroxide. The solution obtained is concentrated and the residue recovered in 1 liter of water. The mixture is brought to boiling with reflux and the insoluble fraction is eliminated. The filtrate obtained is acidified by means of sulfurous anhydride, the solid formed is centrifuged, washed in water, dried, and made to

recrystallize in 100 ml of benzene. 16 g (51%) of (diphenyl-4,5 oxazolyl)-2 thio / acetic acid is obtained. (F = 138°C).

Analysis: $C_{17}H_{13}NO_3S$

calculated: C% 65.6 H% 4.2 N% 10.3

found: 65.5 H% 4.2 N% 10.4

Example 2: {bis (paramethoxyphenyl-4,5 oxazolyl)-2 thio /acetic acid:

A/ {bis (paramethoxyphenyl-4,5 oxazolyl)-2 thio /acetic acid:

A solution of 10 g (0.084 mole) of mercapto-2 ethyl acetate in 100 ml of dimethyl formamide is added under agitation at 25°C to a suspension of sodium hydride produced by using 3.84 g (0.08 mole) of a 50% dispersion of sodium hydride in paraffin oil . The agitation is continued for one hour and a solution of 25.3 g (0.08 mole) of /12 chloro-2 (paramethoxyphenyl)-4, 5-oxazole in 100 ml of dimethyl formamide is added at ambient temperature. The agitation is maintained for two hours and the solvent is eliminated under reduced pressure.

The residue is put into water and ether, the etherized phase, which is washed in water, is separated, dried, and concentrated. An oil (26.3 g) is obtained, brought to boiling with reflux for three hours in the mixture formed by 250 ml of 95° ethanol and 4 g (0.071 mole) of potassium hydroxide. The alcohol is eliminated and the residue is put into water. The acid that precipitates is extracted by means of chloroform, the organic phase is washed in water, dried, the solvent is eliminated, and the solid product obtained is recrystallized in 100 ml of methanol.

5.3 g (14.6%) of bis(paramethoxyphenyl-4,5 oxazolyl)-2 thio /acetic acid is obtained. (F = 140°C).

Analysis: $C_{19}H_{17}NO_5S$

calculated:	C%	61.4	H%	4.6	S% 8.6
found:		61.5		4.7	8.6

B/ Production of chloro-2 bis (paramethoxyphenyl)-4,5 oxazole:

a) bis (paramethoxyphenyl)-4,5 oxazole one-2:

The mixture formed by 220 g (0.81 mole) of anisoine and 350 g (4 moles) of ethyl carbamate by distilling the water and alcohol formed is agitated for eight hours in an oil bath heated to 220 °C. After cooling, it is poured into 1 liter of water and the product formed is centrifuged. It is washed in water, dried under a vacuum in the presence of phosphoric anhydride, and the product obtained is made to recrystallize in the mixture of dimethyl formamide and water (9/1). 170 g (17%) of bis (paramethyoxyphenyl)-4,5 oxazoline-4 one-2 is obtained. (F = 220°C).

Analysis: $C_{17}H_{15}NO_4$

calculated:	C%	68.7	H%	5.1	N% 4.7
found:		68.8		5.1	4.7

b) chloro-2 bis (paramethoxyphenyl)-4,5 oxazole:

A mixture of 118 g (0.4 mole) of bis (paramethoxyphenyl)-4,5 oxazoline- 4 one-2, 330 ml of phosphorous oxychloride, and 40.4 g (0.4 mole) of triethyl amine are brought to boiling with reflux for fifteen hours. The solution is cooled and the precipitate formed at the time of cooling is dissolved in 250 ml of chloroform. The solvents are

eliminated under reduced pressure and the residue is poured into 500 ml of water. The product is extracted by 3 times 250 ml of /13 chloroform, the organic phase is washed in water, dried, and concentrated.

The product obtained is made to recrystallize in 1,200 ml of isopropyl oxide. 90 g (71%) of chloro-2 bis (paramethoxyphenyl)-4,5 oxazole is obtained. (F = 116°C).

Analysis: $C_{17}H_{14}ClNO_3$

calculated:	C%	64.7	H%	4.5	N%	4.4	Cl% 11.2
found:		64.5		4.5		4.3	11.0

Example 3: (diphenyl-4,5 oxazolyl)-2 oxyacetic acid:

a) (diphenyl-4,5 oxazolyl)-2 ethyl oxyacetate:

A suspension of sodium hydride is produced in 50 ml of dimethyl formamide by using 5.81 g (0.12 mole) of sodium hydride in a 50% dispersion of paraffin oil. A solution of 12.5 g (0.2 mole) of ethyl glycolate in 100 ml of dimethyl formamide is added to this suspension. It is agitated for one hour at room temperature and a solution of 25.6 g (0.1 mole) of chloro-2 diphenyl-4,5 oxazole in 50 ml of dimethyl formamide is added. The mixture is agitated for two hours and the solvent is eliminated under reduced pressure. The residue is put into 500 ml of water. The precipitate formed is centrifuged, it is washed in water, and dried. It is made to recrystallize in 300 ml of heptane. 25.3 g (78%) of (diphenyl-4,5 oxazolyl)- 2 ethyl oxyacetate is obtained. (F = 118°C).

Analysis: $C_{17}H_{13}NO_4$

calculated:	C%	69.2	H%	4.4	N% 4.7
found:		69.4		4.7	4.7

Example 4: /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxyacetic acid: /14

a) /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 ethyl oxyacetate:

Operating as indicated in paragraph a) of Example 3, but using 30 g (0.099 mole) of chloro-2 bis (paramethoxyphenyl)-4,5 oxazole (produced as is indicated in Example 2), 5.8 g (16%) of /bis(paramethoxy phenyl)-4,5- oxazolyl/-2 ethyl acetate is obtained, which is made to recrystallize in isopropanol.

(F = 132°C)

Analysis: $C_{21}H_{21}NO_6$

calculated:	C%	65.8	H%	5.5	N% 3.7
found:		65.4		5.8	3.6

b) /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 ethyl oxyacetic acid :

Operating as indicated in paragraph a) of Example 3, but using 5.6 g (0.015 mole) of /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 ethyl oxyacetate, 3.8 g (73%) of /bis (paramethoxy phenyl)-4,5- oxazolyl/-2 oxyacetic acid is obtained, which is made to recrystallize in ethanol. (F = 130°C)

Analysis: $C_{19}H_{17}NO_6$

calculated:	C%	64.2	H%	4.8	N% 3.9
found:		64.2		4.9	3.8

Example 5: (parachlorophenyl)-4 oxazolyl)-2 oxyacetic acid:

A) (parachlorophenylenyl-4 oxazolyl)-2 oxyacetic acid:

a) (parachlorophenylenyl-4 oxazolyl)-2 ethyl acetate:

Operating as indicated in paragraph a) of Example 3, but using 27.5 g (0.129 mole) of (chloro-2 parachlorophenyl)-4 oxazole, 18.2 g (50%) of (parachlorophenyl)-4 oxazolyl)-2 ethyl acetate is obtained, which is made to recrystallize in hexane. /15 (F = 64°C)

Analysis: $C_{13}H_{12}ClNO_4$

calculated:	C%	55.4	H%	4.3	Cl% 12.6
found:		55.6		4.4	12.6

b) (parachlorophenylenyl-4 oxazolyl)-2 oxyacetic acid:

Operating as indicated in paragraph a) of Example 3, but using 17.7 g (0.063 mole) of (parachlorophenyl-4 oxazolyl)-2 ethyl acetate, 14.4 g (90%) of (parachlorophenyl-4 oxazolyl)-2 oxyacetic acid is obtained, which is purified by recrystallization in ethanol (F = 136°C)

Analysis: $C_{11}H_8ClNO_4$

calculated:	C%	52.1	H%	3.2	N% 5.5
found:		51.9		3.2	5.3

B) Production of chloro-2 parachlorophenyl-4 oxazole:

a) parachlorophenyl-4 oxazoline-4 one-2

The mixture of 57 g (0.335 mole) of chloro-4' hydroxy-2 acetophenone and 150 g (1.7 mole) of ethyl carbamate is agitated for eight hours in an oil bath heated to 220°C, distilling the water and

alcohol formed.

After cooling, 1 liter of water is added and the product formed is centrifuged. It is washed with water, dried under a vacuum in the presence of phosphoric anhydride, and recrystallized in 300 ml of acetonitrile. 12.5 g (19%) of parachlorophenyl-4 oxazoline-4 one-2 is obtained. (F= 240°C).

Analysis: $C_9H_6ClNO_2$

calculated:	C%	55.3	H%	3.1	N% 7.2	Cl%	18.1
found:		55.5		3.2	7.1		17.9

b) chloro-2 parachlorophenyl-4 oxazole:

Operating as indicated in paragraph B, b) of Example 2, but heating 0.25 mole of parachlorophenyl-4 oxazoline-4 one-2, 210 ml of phosphorous oxychlorate, and 25.5 g (0.25 mole) of triethylamine /16 to the boiling point with reflux for two hours, 27.5 g (51%) (Eb 0.02 = 110°C) of chloro-2 parachlorophenyl-4 oxazole is distilled, which is solidified by cooling. (F = 74°C).

Analysis: $C_9H_6Cl_2NO$

calculated:	C%	50.5	H%	2.4	N% 7.5	Cl%	33.1
found:		50.4		2.5	7.6		33.5

Example 6: /bis(parachlorophenyl)-4,5 oxazolyl/-2 oxyacetic acid:

A) /bis(parachlorophenylenyl)-4,5 oxazolyl/-2 oxyacetic acid:

a) /bis(parachlorophenylenyl)-4,5 oxazolyl)-2 ethyl acetate:

Operating as indicated in paragraph a) of Example 3, but using 18 g (0.055 mole) of chloro-2 bis (parachlorophenyl)-4,5 oxazole, 14.2 g (67%) of / bis(parachlorophenyl)-4,5 oxazolyl/-2 ethyl

acetate is obtained, which is made to recrystallize in heptane. (F = 100°C-103°C)

Analysis: $C_{19}H_{15}Cl_2NO_4$

calculated:	C%	58.2	H%	3.9
found:		58.4		3.6

b) /bis(parachlorophenylenyl/-4,5 oxazolyl/-2 oxyacetic acid:

Operating as indicated in paragraph b) of Example 3, but using 12 g (0.030 mole) of /bis (parachlorophenyl)-4,5 oxazolyl/-2 ethyl acetate, 2.1 g (19%) of /bis (parachlorophenyl-4,5 oxazolyl)-2 oxyacetic acid is obtained, which is made to recrystallize in isopropanol. (F = 132°C - 138°C).

Analysis: $C_{17}H_{11}Cl_2NO_4$

calculated:	C%	56.1	H%	3.0	Cl% 19.5
found:		56.1		3.2	19.8

B/ Production of chloro-2 bis (parachlorophenyl-4,5 oxazole:

Operating as indicated in paragraph B, b) of Example 2, but heating 53.8 g (0.176) mole of bis (parachlorophenyl)-4,5 oxazoline-4 one-2, 145 ml of phosphorous oxychlorate, and 17.5 g (0.176 mole) of triethylamine to the boiling point with reflux for ten hours, 45 g (70%) of chloro-2 bis (parachlorophenyl)-4,5 oxazole is obtained, which is made to recrystallize in heptane. (F = 125°C).

Analysis: $C_{15}H_8Cl_3NO_4$

calculated:	C%	55.5	H%	2.5	Cl% 32.8
found:		55.6	H%	2.6	32.0

Example 7: (parachlorophenyl-4 methyl-5 oxazolyl)-2 oxyacetic acid:

A/ (parachlorophenyl-4 methyl-5 oxazolyl)-2 oxyacetic acid: /17

Operating as indicated in paragraph A of Example 2, but using 26 g (0.25 mole) of ethyl glycolate and 47 g (0.206 mole) of (chloro-2 parachlorophenyl)-4 methyl-5 oxazole, 15.2 g (27%) of (parachlorophenyl)-4 methyl-5 oxazolyl)-2 oxyacetic acid is obtained, which is made to recrystallize in benzene. (F = 122°C)

Analysis: $C_{12}H_{10}ClNO_4$

calculated:	C%	53.8	H%	3.8	N%	5.2	Cl% 13.2
found:		53.8		3.9		5.2	13.2

B/ Production of chloro-2 parachlorophenyl-4 methyl-5 oxazole:

a) parachlorophenyl-4 methyl-5 oxazoline-4 one-2:

Operating as indicated in paragraph B, a) of Example 5, but using 184 g (1 mole) of chloro-4' hydroxy-2 propiophenone and 89 g (1 mole) of ethyl carbamate, 71 g (34%) of parachlorophenyl-4 methyl-5 oxazoline-4 one-2 is obtained, which is made to recrystallize in methanol. (F = 220°C).

Analysis: $C_{10}H_8ClNO_2$

calculated:	C%	57.3	H%	3.8	N%	6.7
found:		57.2		4.0		6.5

b) chloro-2 parachlorophenyl-4 methyl-5 oxazole:

Operating as indicated in paragraph B, b) of Example 2, but heating 54.5 g (0.26 mole) of parachlorophenyl-4 methyl-5 oxazoline-4 one-2, 215 ml of phosphorous oxychlorate, and 26.5 g (0.26 mole) of triethylamine to the boiling point with reflux for two hours, 31 g

(52%) of chloro-2 parachlorophenyl-4 methyl-5 oxazole (Eb 0.02 = 116°C-120°C) is distilled, which is solidified by cooling. (F = <45°C).

Analysis: $C_{10}H_7Cl_2NO$

calculated:	C%	52.7	H%	3.1	N%	6.1	Cl% 31.1
found:		52.6		3.0		6.0	31.2

Example 8: {/bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy} -2 propionic acid:

a) {/bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy} -2 ethyl propionate:

Operating as indicated in paragraph a) of Example 3, but using 24.6 g (0.078 mole) of chloro-2 bis (paramethoxyphenyl)-4,5 oxazole (produced as is indicated in Example 2, B) and 9.3 g (0.079 mole) of ethyl lactate, 11 g (35%) of {bis (paramethoxyphenyl-4,5 oxazolyl)-2 /18 oxy} ethyl propionate is obtained, which is made to recrystallize in isopropanol. (F = 80°C).

Analysis: $C_{22}H_{23}NO_6$

calculated:	C%	66.5	H%	5.8	N%	3.5
found:		66.5		5.6		3.8

b) {/bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy} -2 propionic acid:

Operating as indicated in paragraph b) of Example 3, but using 8 g (0.020 mole) of {/bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy}-2 ethyl propionate, 4.4 g (59%) of {/bis (paramethoxyphenyl-4,5 oxazolyl/-2 oxy}-2 propionic acid is obtained, which is made to recrystallize in isopropanol. (F = 120°C).

Analysis: $C_{20}H_{19}NO_6$

calculated:	C%	65.0	H%	5.2	N% 3.8
found:		65.0		5.4	3.6

Example 9: /(parachlorophyenyl-4 oxazolyl)-2 thio/ acetic acid:

a) /(parachlorophenyl-4 oxazolyl)-2 thio/ ethyl acetate:

A suspension of sodium hydride in 50 ml of dimethyl formamide is produced by using 3.4 g (00.71 mole) of sodium hydride in a 50% dispersion in paraffin oil. A solution of 15 g (0.071 mole) of parachlorophenyl-4 mercapto-2 oxazole in 100 ml of dimethyl formamide is added to the mixture while agitating (temperature 20°C). The agitation is maintained at ambient temperature for one hour. Then 12 g (0.071 mole) of ethyl bromacetate is added, drop by drop, while cooling, and the agitation is maintained at 25°C for twelve hours.

The solvent is eliminated under reduced pressure and the residue is recovered with a liter of water. A solid product is obtained which is centrifuged, washed in water, dried, and made to recrystallize in 150 ml of cyclohexane. 11.5 g (56%) of /(parachlorophenyl-4 oxazolyl)-2 thio/ ethyl acetate is obtained (F = 76°C).

Analysis: $C_{13}H_{12}ClNO_3S$

calculated:	C%	52.4	H%	4.1	S% 10.8
found:		52.3		4.1	10/6

b) /(parachlorophyenyl-4 oxazolyl)-2 thio/ acetic acid:

The mixture of 11 g (0.037 mole) of /(parachlorophenyl-4 oxazolyl)-2 thio/ ethyl acetate, 2 g (0.05 mole) of sodium hydroxide, and 200 ml of 95° ethanol are brought to a boil with reflux for /19

one hour. The ethanol is eliminated under reduced pressure and the residue is recovered with water. The aqueous phase is washed with ether and acidified by means of sulfurous anhydride. The precipitate formed is centrifuged, washed with water, dried, and made to recrystallized in 35 ml of benzene. 6.3 g (63%) of /(parachlorophenyl-4 oxazolyl)-2 thio/ acetic acid is obtained (F = 130°C).

Analysis: $C_{11}H_8ClNO_3S$

calculated:	C%	49.0	H%	3.0	S%	11.0	Cl%	13.1
found:		48.8		3.1		11.9		13.1

B/ Production of parachlorophenyl-4 mercapto oxazole:

A mixture of 34.1 g (0.2 mole) of chloro-4' hydroxy-2 acetophenone, 29 g (0.3 mole) of potassium thiocyanate, 400 ml of 95° alcohol, and 30 ml of concentrated hydrochloric acid is brought to a boil with reflux for twenty-four hours. The hot solution is filtered, 10 ml of water is added, and the product is let to crystallize. It is centrifuged, washed two times with 150 ml of water, dried, and made to recrystallize in 95° alcohol.

33 g (78%) of parachlorophenyl-4 mercapto-2 oxazole is obtained (F = 240°C).

Analysis: C_9H_6ClNOS

calculated:	C%	51.1	H%	2.9	N%	6.6	S%	15.1	Cl% 16.7
found:		50.6		3.0		6.4		15.1	16.5

Example 10: /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ acetic acid:

A/ /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ acetic acid:

a) /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ ethyl acetate:

Operating as indicated in paragraph A, a) of Example 9, but using 14 g (0.062 mole) of parachlorophenyl-4 mercapto-2 methy-5 oxazole and 10.5 g (0.062 mole) of ethyl bromacetate, 5 g (26%) of /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ ethyl acetate is obtained, which is made to recrystallize in hexane. (F = 48°C-53°C).

Analysis: $C_{14}H_{14}ClNO_3S$

calculated:	C%	53.9	H%	4.5	S% 10.3
found:		53.8		4.6	10.1

b/ /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ acetic acid:

Operating as indicated in paragraph A, b) of Example 9, but using 14.5 g (0.046 mole) of /(parachlorophenyl-4 methy-5 oxazolyl)-2 /20 thio/ ethyl acetate, 6.8 g (51%) of /(parachlorophenyl-4 methyl-5 oxazolyl)-2 thio/ acetic acid is obtained, which is made to recrystallize in benzene. (F = 150°C).

Analysis: $C_{12}H_{10}ClNO_3S$

calculated:	C%	50.8	H%	3.6	S% 11.3
found:		51.2		3.7	11.3

B/ Production of parachlorophenyl-4 mercapto-2 methyl-5 oxazole:

A mixture of 18.5 g (0.1 mole) of chloro-4' hydroxy-2 propiophenone, 15 g (0.15 mole) of potassium thiocyanate, 200 ml of 95° ethanol, and 15 ml of concentrated hydrochloric acid is brought to

a boil with reflux for twenty-four hours.

The mixture is cooled, extracted 3 times with 200 ml of chloroform, the organic phase is washed 3 times with 300 ml of water, dried, the chloroform is eliminated under reduced pressure, and the residue (26 g) is made to recrystallize in 200 ml of benzene, and 14.6 g (65%) of parachlorophenyl-4 mercapto-2 methyl-5 oxazole is obtained. (F = 170°C-173°C).

Analysis: $C_{10}H_8ClNOS$

calculated:	C%	53.2	H%	3.6	N%	6.2	S%	14.2	Cl% 15.7
found:		53.3		3.7		6.0		14.4	15.5

Example 11: /(parachlorophenyl-5 oxazolyl)-2 thio/ acetic acid:

A/ /(parachlorophenyl-5 oxazolyl)-2 thio/ acetic acid:

a) /(parachlorophenyl-5 oxazolyl)-2 thio/ ethyl acetate:

Operating as indicated in paragraph A, a) of Example 9, but using 15 g (0.075 mole) of parachlorophenyl-5 mercapto-2 oxazole and 12.7 g (0.075 mole) of ethyl bromacetate, 15.9 g (71%) of /(parachlorophenyl-5 oxazolyl)-2 thio/ ethyl acetate is obtained, which is made to recrystallize in heptane. (F = 90°C).

Analysis: $C_{13}H_{12}ClNO_3S$

calculated:	C%	52.4	H%	4.1	S%	10.8	
found:		52.6		4.3		10.8	

b) /(parachlorophenyl-5 oxazolyl)-2 thio/ acetic acid:

Operating as indicated in paragraph A, b) of Example 9, but using 15.9 g (0.053 mole) of /(parachlorophenyl-5 oxazolyl)-2 thio/ ethyl acetate, 11.4 g (79%) of /(parachlorophenyl-5 oxazolyl)-2 thio/

acetic acid is obtained, which is made to recrystallize in benzene. (F = 159°C).

Analysis: $C_{11}H_8ClNO_3S$ /21

calculated:	C%	49.0	H%	3.0	N%	5.2	S% 11.9
found:		49.1		3.2		5.0	11.8

B/ Production of parachlorophenyl-5 mercapto-2 oxazole:

A mixture of 20.6 g (0.1 mole) of amino-2 chloro-4' acetophenone chlorhydrate, 15.2 g (0.2 mole) of carbon sulfide, 10.6 g (0.1 mole) of sodium carbonate, 150 ml of ethanol, and 30 ml of water is brought to a boil with reflux for twelve hours. The solution is filtered, then the filtrate is acidified by means of sulfurous anhydride. The precipitate formed is centrifuged and washed with 100 ml of ethanol. The product is made to recrystallize in 300 ml of ethanol. 7.7 g (36%) of parachlorophenyl-5 mercapto-2 oxazole are obtained. (F = 285°C).

Analysis: C_9H_6ClNOS

calculated:	S %	15.1	Cl%	16.7
found:		15.3		16.6

Example 12:

Tablets corresponding to the following formula were produced:

- /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 thio acetic acid 200 mg
- excipient q.s. for a tablet:

(details of the excipient: lactose, starch, talc, magnesium stearate)

Example 13:

Tablets corresponding to the following formula were produced:

- /bis(paramethoxyphenyl)-4,5 oxazolyl/-2 oxy-2 propionic acid 200mg
- excipient q.s. for a tablet:

(details of the excipient: lactose, starch, talc, magnesium stearate)

Example 14:

Tablets corresponding to the following formula were produced:

- /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxyacetic acid 200 mg
- excipient q.s. for a tablet:

(details of the excipient: lactose, starch, talc, magnesium stearate)

Example 15:

Tablets corresponding to the following formula were produced:

- (parachlorophenyl)-4 methyl-5 oxazolyl/-2 oxyacetic acid 200 mg
- excipient q.s. for a tablet: /22

(details of the excipient: lactose, starch, talc, magnesium stearate)

Example 16:

Tablets corresponding to the following formula were produced:

- (parachlorophenyl)-4 oxazolyl/-2 oxyacetic acid 200 mg
- excipient q.s. for a tablet:

(details of the excipient: lactose, starch, talc, magnesium stearate)

Example 17:

An ointment corresponding to the following formula was produced:

- /bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxyacetic acid 2 g
- excipient q.s. for 100 g

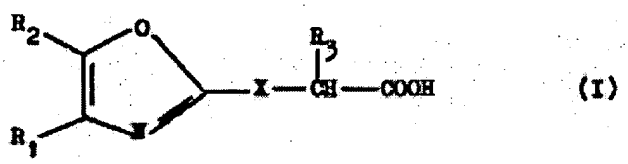
Example 18:

An ointment corresponding to the following formula was produced:

- (parachlorophenyl)-4 oxazolyl/-2 oxyacetic acid 2 g
- excipient q.s. for 100 g

CLAIMS /23

1. An oxyazole derivative as well as metallic salts thereof, addition salts with nitrogenated bases thereof, and esters thereof with alcohols, containing at most 4 carbon atoms, these derivatives being characterized by the fact that they correspond to the general formula:



(I)

in which X represents an oxygen or sulfur atom, R_1 represents a hydrogen atom, or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, R_2 represents a hydrogen atom or an alkyl radical containing at most 3 carbon atoms or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, R_3 represents a hydrogen atom, or an alkyl radical containing at most 3 carbon atoms.

2. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 thioacetic acid.

3. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy-2 propionic acid.

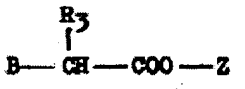
4. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxyacetic acid.

5. (Parachlorophenyl)-4, methyl-5 oxazolyl/-2 oxyacetic acid.

6. (Parachlorophenyl)-4, oxazolyl/-2 oxyacetic acid.

7. /Bis (parachlorophenyl)-4,5 oxazolyl/-2 oxyacetic acid.

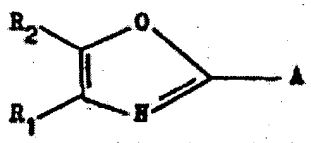
8. A method of producing derivatives defined by formula I of Claim 1, wherein a product of the following formula is sodified:



(II)

in which B represents a radical -OH or a radical -SH, Z an alkyl radical containing at most 4 carbon atoms, and R_3 has the meaning already indicated, then this sodified product is made to react with a product of the following formula:

/24



(III)

in which R_1 and R_2 have the meaning already indicated and A represents a chlorine atom, then an alkaline hydroxyl is used to hydrolyze the product of the following formula:

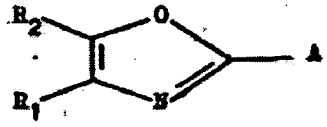
(IV)

in which R_1, R_2, R_3, X, and Z have the meaning already indicated, thus obtained in order to obtain the product of formula I.

9. The method according to Claim 8, wherein the product of formula II, in which B represents an -OH radical or an -SH radical, is

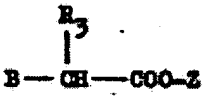
sodified by sodium ethylate or sodium hydride.

10. A method of producing derivatives defined by formula I of Claim 1, in which X represents a sulfur atom, wherein a product of the following formula is sodified:



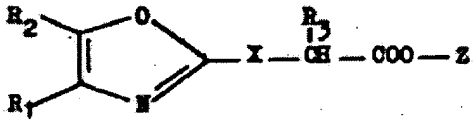
(III)

in which R_1 and R_2 have the meaning already indicated and A represents a radical -SH, then this sodafied product is made to react with a product of the following formula:



(II)

in which R represents a chlorine or bromine atom, Z represents an alkyl radical including at most 4 carbon atoms, and R_3 has the meaning already indicated, then the product of the following formula is hydrolyzed by means of an alkaline hydroxide :



(IV)

in which R_1, R_2, R_3, X, and Z have the meaning already indicated, /25 thus obtained, in order to obtain the product of formula I.

11. The method according to Claim 10, wherein the product of formula III in which A represents an -SH radical is sodified by sodium ethylate or by sodium hydride.

12. A method of producing metallic salts and addition salts with nitrogenated bases of derivatives defined by formula I of Claim 1,

wherein the corresponding mineral or nitrogenated bases are made to act on these derivatives of formula I.

13. A method of producing esters with alcohols containing at most 4 carbon atoms of derivatives defined by formula I of Claim 1, wherein an alcohol containing at most 4 carbon atoms is made to act on these derivatives of formula I in the presence of an acid catalyst.

14. A method of producing esters of derivatives defined by formula I of Claim 1, which consists in producing the product of formula IV according the method described in Claim 8 or 10, and wherein this product of formula IV, then obtained, is isolated.

15. Medications, and, in particular, anti-inflammatory, analgesic, and anti-pyretic medications, wherein they consist of derivatives corresponding to formula I of Claim 1, or pharmaceutically acceptable metallic salts, addition salts with nitrogentated bases, or esters with alcohols containing at most 4 carbon atoms .

16. Medications, and, in particular, anti-inflammatory, analgesic, and anti-pyretic medications, wherein they consist of oxazole derivatives defined in Claims 2 to 7 or by pharmaceutically acceptable metallic salts thereof, addition salts thereof with nitrogenated bases, or esters thereof with alcohols containing at most 4 carbon atoms.

17. Pharmaceutical compositions, wherein they contain at least one of the medications as defined in Claims 15 and 16 as active principle.

18. As useful new commercial products, in particular for producing derivatives corresponding to formula I of Claim 1, the following substituted chloro-2 oxazoles: chloro-2 bis /26
(paramethoxyphenyl)-4,5 oxazole, chloro-2 parachlorophenyl-4 methyl-5 oxazole, chloro-2 parachlorophenyl-4 oxazole, chloro-bis (parachlorophenyl)-4,5 oxazole, and the following substituted mercapto-2 oxazoles: parachlorophenyl-4 mercapto-2 oxazole, parachlorophenyl-4 mercapto-2 methyl-5 oxazole, and parachlorophenyl-5 mercapto-2 oxazole.

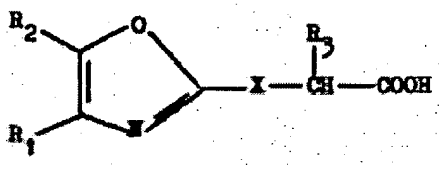
Example 18:

An ointment corresponding to the following formula was produced:

- (parachlorophenyl)-4 oxazolyl/-2 oxyacetic acid 2 g
- excipient q.s. for 100 g

CLAIMS /23

1. An oxyazole derivative as well as metallic salts thereof, addition salts with nitrogenated bases thereof, and esters thereof with alcohols, containing at most 4 carbon atoms, these derivatives being characterized by the fact that they correspond to the general formula:



(I)

in which X represents an oxygen or sulfur atom, R_1 represents a hydrogen atom, or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, R_2 represents a hydrogen atom or an alkyl radical containing at most 3 carbon atoms or a phenyl radical, or a phenyl radical substituted either by a fluorine, chlorine, or bromine atom, or by an alkoxy radical containing at most 3 carbon atoms, R_3 represents a hydrogen atom, or an alkyl radical containing at most 3 carbon atoms.

2. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 thioacetic acid.

3. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxy-2 propionic acid.

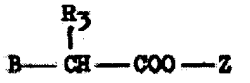
4. /Bis (paramethoxyphenyl)-4,5 oxazolyl/-2 oxyacetic acid.

5. (Parachlorophenyl)-4, methyl-5 oxazolyl/-2 oxyacetic acid.

6. (Parachlorophenyl)-4, oxazolyl/-2 oxyacetic acid.

7. /Bis (parachlorophenyl)-4,5 oxazolyl/-2 oxyacetic acid.

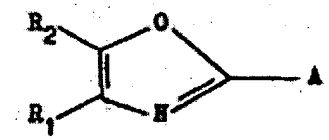
8. A method of producing derivatives defined by formula I of Claim 1, wherein a product of the following formula is sodified:



(II)

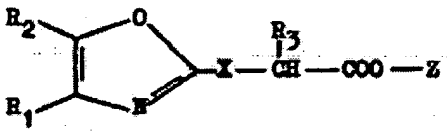
in which B represents a radical -OH or a radical -SH, Z an alkyl radical containing at most 4 carbon atoms, and R_3 has the meaning already indicated, then this sodified product is made to react with a product of the following formula:

/24



(III)

in which R_1 and R_2 have the meaning already indicated and A represents a chlorine atom, then an alkaline hydroxyl is used to hydrolyze the product of the following formula:



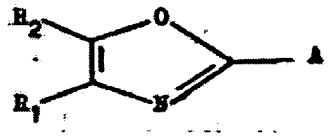
(IV)

in which R_1, R_2, R_3, X, and Z have the meaning already indicated, thus obtained in order to obtain the product of formula I.

9. The method according to Claim 8, wherein the product of formula II, in which B represents an -OH radical or an -SH radical, is

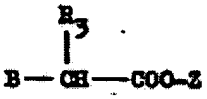
sodified by sodium ethylate or sodium hydride.

10. A method of producing derivatives defined by formula I of Claim 1, in which X represents a sulfur atom, wherein a product of the following formula is sodified:



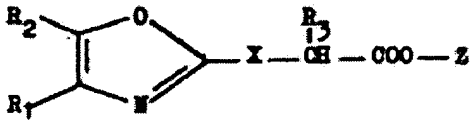
(III)

in which R_1 and R_2 have the meaning already indicated and A represents a radical -SH, then this sodafied product is made to react with a product of the following formula:



(II)

in which R represents a chlorine or bromine atom, Z represents an alkyl radical including at most 4 carbon atoms, and R_3 has the meaning already indicated, then the product of the following formula is hydrolyzed by means of an alkaline hydroxide :



(IV)

in which R_1, R_2, R_3, X, and Z have the meaning already indicated, /25 thus obtained, in order to obtain the product of formula I.

11. The method according to Claim 10, wherein the product of formula III in which A represents an -SH radical is sodified by sodium ethylate or by sodium hydride.

12. A method of producing metallic salts and addition salts with nitrogenated bases of derivatives defined by formula I of Claim 1,

wherein the corresponding mineral or nitrogenated bases are made to act on these derivatives of formula I.

13. A method of producing esters with alcohols containing at most 4 carbon atoms of derivatives defined by formula I of Claim 1, wherein an alcohol containing at most 4 carbon atoms is made to act on these derivatives of formula I in the presence of an acid catalyst.

14. A method of producing esters of derivatives defined by formula I of Claim 1, which consists in producing the product of formula IV according the method described in Claim 8 or 10, and wherein this product of formula IV, then obtained, is isolated.

15. Medications, and, in particular, anti-inflammatory, analgesic, and anti-pyretic medications, wherein they consist of derivatives corresponding to formula I of Claim 1, or pharmaceutically acceptable metallic salts, addition salts with nitrogentated bases, or esters with alcohols containing at most 4 carbon atoms .

16. Medications, and, in particular, anti-inflammatory, analgesic, and anti-pyretic medications, wherein they consist of oxazole derivatives defined in Claims 2 to 7 or by pharmaceutically acceptable metallic salts thereof, addition salts thereof with nitrogenated bases, or esters thereof with alcohols containing at most 4 carbon atoms.

17. Pharmaceutical compositions, wherein they contain at least one of the medications as defined in Claims 15 and 16 as active principle.

18. As useful new commercial products, in particular for producing derivatives corresponding to formula I of Claim 1, the following substituted chloro-2 oxazoles: chloro-2 bis /26
(paramethoxyphenyl)-4,5 oxazole, chloro-2 parachlorophenyl-4 methyl-5 oxazole, chloro-2 parachlorophenyl-4 oxazole, chloro-bis (parachlorophenyl)-4,5 oxazole, and the following substituted mercapto-2 oxazoles: parachlorophenyl-4 mercapto-2 oxazole, parachlorophenyl-4 mercapto-2 methyl-5 oxazole, and parachlorophenyl-5 mercapto-2 oxazole.